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09/629,719	08/01/2000	Teruna J. Siahaan	30406	5579

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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/629,719	Applicant(s) SIAHAAN ET AL.	
	Examiner Maher M. Haddad	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 35-42* is/are pending in the application.

4a) Of the above claim(s) *4-5 and 39-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-9, 35-38 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-9 and 35-42 are pending.

2. Applicant's election of Group I, claims 1-9 (now claims 1-9 and 35-42), in Paper No. 14 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant elected SEQ ID NO:8 (cIBR), derived from ICAM-1 and methotrexate as the species. Claims 1-3, 6-9, 35-38 and 42 read on the elected species.

3. Claims 4-5 and 39-41 (non-elected species of the elected Group I) are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 1-3, 6-9, 35-38 and 42 are under examination as they read on an a conjugate comprising a drug coupled with an isolated peptide sequence, wherein the peptide is SEQ ID NO:8 and the drug is methotrexate as the species.

5. The formal drawings submitted 8/20/02 (paper No. 15) have been approved by the Draftsman. Further, the petition to accept color drawings filed 8/01/00 is hereby granted. The specification should be amended to insert the following paragraph:

"The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee".

6. The amendment filed 07/03/02 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The preliminary amendment filed on 07/03/02 to the Sequence Listing and computer readable Form substituting the original Sequence Listing represents a departure from the specification and the claims as originally filed. Applicant does not points out for support for the newly added limitation "Xaa is penicillamine". However, the specification and the claims as originally filed have no support for the new added matter "Xaa is penicillamine". It is noted in the specification, page 17, line 16 that SES ID NO:2 shows show N-terminal Pen, however, no support was found for other SEQ ID NOS: 1 and 3-8.

Applicant is required to cancel the new matter in the response to this Office action.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 2 is indefinite for reciting "from about 4-30 amino acid residues" in line 2. It is unclear how many amino acids constitute "about".

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 36-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The conjugate comprising a drug coupled with an isolated peptide sequence, wherein said peptide sequence including "at least one non-natural amino acid" in claim 36 and said "non-natural amino acid being penicillamine" claimed in claim 37 represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 8/20/02 points to the specification in sequence listing of SEQ ID NOS: 2, 3, 4, 6-9 for support for the newly added limitations "at least one non-natural amino acid" and " non-natural amino acid being penicillamine". However, the specification does not provide a clear support of "at least one non-natural amino acid" and " non-natural amino acid being penicillamine". The instant claims now recite limitations which were not clearly disclosed in the specification and claims as originally filed.

11. Claims 1-3, 6-9, 35-38 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a conjugate comprising a methotrexate (MTX) and the drugs recited in claim 7 coupled with a peptide of SEQ ID NO: 1-8 which derived from ICAM-1 and LFA-1; does not reasonably provide **enablement** for **any conjugate** comprising **any drug** coupled with **any isolated peptide** sequence selected from the group consisting of peptide sequences derived from ICAM-1 and LFA-1 in claim 1, wherein said isolated peptide sequence

having from a bout 4-30 amino acid residues in claim 2, wherein said isolated peptide sequence is SEQ ID NO: 8 in claim 3, wherein said peptide differing from that of said isolated peptide sequence of SEQ ID NO:8 due to a mutation event in claim 4, wherein mutation event being selected from the group consisting of point mutations, deletions, insertions and rearrangements in claim 5, wherein said isolated peptide sequence **having** at least about 50% homology with SEQ ID NO:8 in claim 9, wherein isolated peptide sequence including at least one non-natural amino acid in claim 36, wherein non-natural amino acid being penicillamin in claim 37, wherein isolated peptid sequence being cyclic in claim 38, wherein said drug selected from a class of drugs **any** antitumor agents in claim 6, wherein said drug is Methotrexate in claims 7 and 8, wherein said conjugate characterized by the ability of binding to **any** surface receptor of target cells and subsequently being internalized by said target cells in claim 35, or any conjugate comprising a first portion and a second portion, said first portion **comprising any** peptide and said second portion **comprising any** drug, said peptide being derived from ICAM-1 or LFA-1 and being characterized by binding to LFA-1 or ICAM-1 receptors on leukocytes and by being internalized by cells expressing at least one of said receptors in claim 42. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only one drug conjugate MTX-cIBR of SEQ ID NO:8 with a disclosed activity of binding with the cells expressing LFA-1 surface receptors and subsequently being internalized and kill the cells (page 21 line 34 through page 21 line 1). The instant claims encompass in their breadth *any* conjugate comprising any peptide and comprising any drug, wherein the peptide "having at least about 50% homology".

There does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various conjugates comprising various drags coupled with various peptides recited in the instant claims. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance to direct a person of skill in the art to select particular sequences or sequence lengths as essential for binding to surface receptors of target cells and subsequently being internalized by the targeted cells. Without detailed direction as to which peptide sequences are essential to the function of the conjugate, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of peptide sequences encompassed by the instant claims would share the ability to bind a surface receptor and hence internalized, wherein the peptide having at least 50% homology with peptide of SEQ ID NO:8, other than the peptide of SEQ ID NO:8.

Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in

situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Finally, even single amino acid differences can result in drastically altered functions between two proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). Thus it is unpredictable if any functional activity will be shared by two peptides having less than 100% identity over the full length of their sequences.

The term "comprising" in claim 42 is open-ended, it expands the amino acid sequence of SEQ ID NO: 8 to include additional non disclosed amino acids out side of the "binding to LFA-1 receptor", however there is insufficient guidance as to which amino acid segments within the peptide can be unique and retain a distinct functional capability or "binding to LFA-1 receptor". Ngo *et et* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the amino acid sequence of a polypeptide determined its structural property, predictability of which amino acid fragment can retain the functional capabilities of the binding to LFA-1 receptor-comprising polypeptide requires knowledge of, and guidance with regard to, which segments in the peptide's sequence contribute to its function.

Minor structural differences among structurally related compounds or compositions can result in substantially different biological activities, Therefore, structurally unrelated compounds comprising any peptide binding to LFA-1 receptor would be expected to have greater differences in their activities.

Therefore, there is insufficient direction or objective evidence as to how to make and to how to use any conjugate comprising any drug coupled to any peptide derived from ICAM-1 which can be used as target delivery of drug in LFA-1 expressing leukocytes for the number of possibilities associated with the myriad of direct and indirect effects associated with various "conjugate" and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the instantly recited peptide sequences and still maintains the functional properties of the polypeptide of SEQ ID NO:8 is unpredictable, as is the identity of which mutated peptides would have the same functional peptide; thus the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims it would take undue trials and errors to practice the claimed invention.

12. Claims 1-3, 6-9, 35-38 and 42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a conjugate comprising a methotrexate (MTX) and the drugs recited in claim 7 coupled with the peptide of SEQ ID NO: 1-8 which derived from ICAM-1 and LFA-1.

Applicant is not in possession of any conjugate comprising any drug coupled with any isolated peptide sequence selected from the group consisting of peptide sequences derived from ICAM-1 and LFA-1 in claim 1, wherein said isolated peptide sequence having from a bout 4-30 amino acid residues in claim 2, wherein said isolated peptide sequence is SEQ ID NO: 8 in claim 3, wherein said peptide differing from that of said isolated peptide sequence of SEQ ID NO:8 due to a mutation event in claim 4, wherein mutation event being selected from the group consisting of point mutations, deletions, insertions and rearrangements in claim 5, wherein said isolated peptide sequence having at least about 50% homology with SEQ ID NO:8 in claim 9, wherein isolated peptide sequence including at least one non-natural amino acid in claim 36, wherein non-natural amino acid being penicillamin in claim 37, wherein isolated peptid sequence being cyclic in claim 38, wherein said drug selected from a class of drugs any antitumor agents in claim 6, wherein said drug is Methotrexate in claims 7 and 8, wherein said conjugate characterized by the ability of binding to any surface receptor of target cells and subsequently being internalized by said target cells in claim 35, or any conjugate comprising a first portion and a second portion, said first portion comprising any peptide and said second portion comprising any drug, said peptide being derived from ICAM-1 or LFA-1 and being characterized by binding to LFA-1 or ICAM-1 receptors on leukocytes and by being internalized by cells expressing at least one of said receptors in claim 42.

Applicant has disclosed only one drug conjugate comprising MTX coupled with a peptide of SEQ ID NO: 1; therefore, the skilled artisan cannot envision all the contemplated drug cojugate possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35

U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-3, 6-9, 35-38 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gursoy *et al* (April 1999) (IDS reference No.2) in view of Nagy *et al* (1993).

Gursoy *et al* teach a conjugate comprising a 12 amino acid cyclic peptide consisting of SEQ ID NO: 8, that is Cyclo (1, 12)-Pen1-Pro2-Arg3-Gly4-Gly5-Ser6-Val7-Leu8-Val9-Thr10-Gly11-Cys12-OH (cIBR) having 100% homology to SEQ ID NO: 8 and derived from ICAM-1, and a fluorescence-labeled peptide (FITC-cIBR). The conjugate characterized by the ability of binding to surface receptor of target leukocyte Molt-3 T cells and subsequently being internalized by said target cells. Gursoy et al further teach that the peptide of the conjugate include at least one non-natural amino acid penicillamin at amino acid position 1 (see entire document and page 414 under abstract and page 415 right column 2nd paragraph in particular). Finally Gursoy et al teach that the drug conjugated to a ligand molecule that can bind to receptors on the surface of the target cells so that the drug directed specifically to the target cells that express the receptors. The binding and internalization of cIBR peptide can be ustilized as a method of targeted drug delivery to leukocytes for the treatment of leukocyte-related diseases (see abstract and page 414 left column 2nd paragraph in particular).

The Gursoy *et al* teaching differs from the claimed invention by not expressly disclosing to employ the antitumor agent, methotrexate drug in claims 6, 7 and 8.

Nagy *et al* teach that methotrexate is an antineoplastic agent and chemically suitable for conjugation to peptides (see page 6373, right column 2nd paragraph in particular). Further, Nagy *et al* teach that such conjugates can be used as carrier molecules for different chemotherapeutic agents in cases in which direct action of these peptides on the membrane receptors could be established. (page 6376, right column, paragraph 1 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate the peptide taught by the Gursoy *et al* with the drug methotrexate taught by Nagy *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because methotrexate is chemically suitable for conjugation to peptides and such conjugates can be used as carrier molecules for different chemotherapeutic agents in cases in which direct action of these peptides on the membrane receptors could be established as taught by the Nugy *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
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November 4, 2002

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